

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

CABINET BECKER ET ASSOCIES  
10, rue de Milan  
F-75009 Paris  
FRANCE

Date of mailing (day/month/year) 08 November 2000 (08.11.00)	<b>IMPORTANT NOTIFICATION</b>  International filing date (day/month/year) 09 March 2000 (09.03.00)
Applicant's or agent's file reference B0033WO	
International application No. PCT/EP00/02053	

1. The following indications appeared on record concerning:

☒

the applicant

☒

the inventor

☐

the agent

☐

the common representative

Name and Address

HAGER, Jörg  
27, rue de Gien  
F-91540 Mennecy  
France

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒

the person

☐

the name

☐

the address

☐

the nationality

☐

the residence

Name and Address

INTEGRAGEN, S.A.S.  
Pepiniere Genopole Industries  
CCI Essone, 4 Rue Pierre Fontaine  
France

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person indicated in Box has been recorded as applicant for all designated States  
except the US. The person indicated in Box remains inventor/applicant for the US only.

4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the International Searching Authority

☒

the International Preliminary Examining Authority

☐

the designated Offices concerned

☒

the elected Offices concerned

☐

other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Anman QIU

Telephone No.: (41-22) 338.83.38

003643018

## P A T E N T COOPERATION TREATY

PCT

## NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and  
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

CABINET BECKER ET ASSOCIES  
10, rue de Milan  
F-75009 Paris  
FRANCE

Date of mailing (day/month/year) 31 August 2000 (31.08.00)	<b>IMPORTANT NOTIFICATION</b>  International filing date (day/month/year) 09 March 2000 (09.03.00)
Applicant's or agent's file reference B0033WO	
International application No. PCT/EP00/02053	
Applicant HAGER, Jörg	

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. ☒ **Correction of priority claim.** In accordance with the applicant's notice received on: 21 July 2000 (21.07.00), the following priority claim has been corrected to read as follows:  
 DE 12 March 1999 (12.03.99) 199 11 130.8  
☐ even though the indication of the number of the earlier application is missing.  
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2. ☐ **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:  
☐ even though the indication of the number of the earlier application is missing.  
☐ even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3. ☐ As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4. ☐ **Priority claim considered not to have been made.**  
☐ The applicant failed to respond to the invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.  
☐ The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).  
☐ The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.  
 The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(1B).
5. ☐ In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):
6. A copy of this notification has been sent to the receiving Office and  
☐ to the International Searching Authority (where the international search report has not yet been issued).  
☒ the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. (41-22) 740.14.35	Authorized officer  Marie-José Devillard  Telephone No. (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 31 October 2000 (31.10.00)	<b>Applicant's or agent's file reference</b> B0033WO
<b>International application No.</b> PCT/EP00/02053	<b>Priority date</b> (day/month/year) 12 March 1999 (12.03.99)
<b>International filing date</b> (day/month/year) 09 March 2000 (09.03.00)	
<b>Applicant</b> HAGER, Jörg	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 10 October 2000 (10.10.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Mafla Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 11 JUL 2001

WIPO PCT

Applicant's or agent's file reference <b>B0033WO</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/EP00/02053</b>	International filing date (day/month/year) <b>09/03/2000</b>	Priority date (day/month/year) <b>12/03/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C12Q1/68</b>		
Applicant <b>HAGER, J. et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  <b>10/10/2000</b>	Date of completion of this report  <b>05.07.2001</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Barz, W</b>  Telephone No. <b>+49 89 2399 7320</b>



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02053

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)

**Description, pages:**

1-29 as originally filed

**Claims, No.:**

1-22 as received on 18/05/2001 with letter of 17/05/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02053

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 22.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 22 are so unclear that no meaningful opinion could be formed (*specify*):  
**see separate sheet**
- ☒ the claims, or said claims Nos. 22 are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-20
	No: Claims 21
Inventive step (IS)	Yes: Claims 1-18
	No: Claims 19-21
Industrial applicability (IA)	Yes: Claims 1-21

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/02053

No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**ITEM I:**

The amendments to the claims fulfill the requirements of Article 34 (2)(b) PCT.

**ITEM III:**

**Claim 22** relates to a "method to identify DNA regions that are relevant to a pathological condition or a particular trait", comprising two steps (hybridization of amplified and/or pre-selected nucleic acid populations and separation of fully matched heterohybrids). These steps allow the separation of the DNA regions which are identical between the nucleic acid populations. However, said steps are not sufficient to identify DNA regions that are relevant to said condition or trait. Therefore, claim 22 is neither clear nor supported by the description (Article 6 PCT). Consequently, no opinion will be formulated with respect to the subject-matter of claim 22 (Article 34(4)(a)(i) PCT).

**ITEM V:**

Reference is made to the following documents:

- D1: WO 93 22462 A (UNIV LELAND STANFORD JUNIOR), 11 November 1993;
- D2: PNAS, vol. 93, April 1996, pages 4374-4379, (SMITH AND MODRICH);
- D3: WO 89 12695 A (GENELABS INC), 28 December 1989.

**1. NOVELTY**

**Claim 21** does not meet the requirements of Article 33(2) PCT for the following reasons:

- 1.1 A method of separating identical DNA fragments from complex mixtures of at least two nucleic acid populations, comprising all features of **claim 21** of the present application, is disclosed in documents D2 (abstract; page 4375, left paragraph, line 28 - right paragraph, line 29; figures 1-2) and D3 (abstract; pages 16-20;



figure 4). Therefore, the subject-matter of claim 21 is also not novel.

Although the International Preliminary Examining Authority agrees with the Applicant's argument (provided with his letter dated 17.05.01) that the goals of the methods of D2 (detection of mutations in PCR-amplified DNA fragments) and D3 (isolation of unique sequences from one of two fragment mixtures) are different from that of present claim 21, D2 and D3 nevertheless disclose methods comprising all features of present claim 21 (including the separation of fully-matched heterohybrids from DNA mixtures), thereby destroying novelty (Article 33(2) PCT) of said claim.

- 1.2 In contrast, **claims 1-18** meet the requirements of Article 33(2) PCT, because none of the available prior art documents discloses a method having the same combinations of features as in these claims.
- 1.3 The International Preliminary Examining Authority agrees with the Applicant's argument (provided with his letter dated 17.05.01) that the subject-matter of **claims 19-20** is novel in the sense of Article 33(2) PCT, because the available prior art (including D1) do not disclose kits comprising all features of said claims.

## 2. INVENTIVE STEP

However, **claims 19-20** do not appear to meet the requirements of Article 33(3) PCT for the following reasons:

- 2.1 Compared to document D3, which is considered to represent the closest prior art for claims 19-20, the subject-matter of **claim 19** differs in that the double-stranded adaptor molecules and labelled primer are included into a kit. However, the inclusion of known components into a kit falls within the scope of the customary practice followed by persons skilled in the art. It would therefore be an obvious possibility for the skilled person to include the adaptor molecules and labelled primer of D3 into a kit which is suitable for genetic analysis in accordance with present claim 1. Consequently, the subject-matter of claim 19 appears to lack an inventive step (Article 33(3) PCT).

- 2.2 Similarly, **claim 20** does not appear to meet the requirements of the PCT with respect to inventive step, because its only additional, non-optional feature (means for detection) is also known from document D3 (figures 4-5).
- 2.3 In contrast, **claims 1-18** appear to meet the requirements of Article 33(3) PCT for the following reasons:

Document D1, which is considered to represent the closest prior art for said claims, discloses a GMS method for the identification of identical nucleic acid fragments from a mixture of two nucleic acid populations, comprising steps a), d) and e) of present claim 1 (abstract; page 4, lines 4-32; page 19, line 5 - page 21, line 38; claims 1-3 and 6). Compared to D1, the method of **claim 1** differs by the presence of steps b) and c) (adaptor ligation and amplification). According to the description of the present application (page 1, lines 15-19, page 8, lines 4-9 and 16-21, page 10, lines 17-20, page 14, lines 7-18; page 15, line 20 - page 16, line 12), said difference causes several advantageous effects (increased sensitivity and selectivity, decreased costs, comparison of more than two DNA populations).

Therefore, the technical problem to be solved by **claim 1** of the present invention may be regarded as how to provide an improved (i.e. cheaper, more reliable and more useful) GMS method.

The solution proposed in claim 1 can be considered as involving an inventive step (Article 33(3) PCT), because the available prior art does not appear to contain any indication as to include adaptor ligation and amplification (present steps b) and c) of claim 1) into the known GMS method. Although these steps by themselves are known from the prior art (e.g. from document D3, see abstract, claim 1, and figures 1 and 4), the available prior art does not appear to give any indication to combine these steps with the GMS method of D1. Therefore, it would not be obvious to the skilled person to include steps a)-e) into one method, thereby resulting in the subject-matter of present claim 1.

- 2.4 **Claims 2-18** are dependent on claim 1 and as such also meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/02053

3. INDUSTRIAL APPLICABILITY

The subject-matter of **claims 1-21** appears to be industrially applicable in the sense of Article 33(4) PCT.

4. P-DOCUMENTS

The prior art documents which were published after the priority date, but before the filing date of the present application (listed as "P,Y" documents in the International Search Report) are not relevant for the present application, because they neither disclose nor suggest the subject-matter of present of **claims 1-21**.

**ITEM VII:**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

**ITEM VIII:**

1. **Claim 4** does not fulfill the requirement of conciseness (Article 6 PCT) for the following reason: The expression "from different sources" does not seem to add any feature to the subject-matter of claims 1-3, because it is appears from the description (page 9, line 32; page 10, lines 5-8) that "at least two nucleic acid populations" are always "from at least two sources". Therefore, the feature "from different sources" appears to be essential for the present invention and does not add anything to claim 4, in contrast to the requirement of conciseness.

The International Preliminary Examining Authority agrees with the Applicant's argument that the description of the present application (page 9, line 32; page 10, lines 5-8) specifies that the nucleic acid populations of the present application are

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/02053

from different sources. Therefore, claim 4 does not fulfill the requirement of conciseness (Article 6 PCT).

2. The expression "in a chromosome- and sequence-specific fashion" used in **claim 6** is not clear (Article 6 PCT), because the meaning of said expression is not apparent from the wording of the claim alone (i.e. without reading the description, as required by PCT-Guidelines III-4.2).